REMARKS

The Examiner has rejected claims 12-15 and 19 under 35 U.S.C. § 103 as obvious over Bialer in view of Ross and French. All of these references are of record already, so full citations are not given.

The Examiner asserts that Bialer teaches that "AWD-131-138," the compound recited in the claims treats audiogenic clonic seizures in genetic models of epilepsy. The Examiner concludes that:

> "(B)ecause it is taught that AWD 131-138 has anticonvulsant activities in animal models of epilepsy, it is obviously taught that AWD 131-138 would effectively treat epilepsy regardless of when it was diagnosed."

The skilled artisan that Bialer is teaching idiopathic epilepsy with AWD-131-138.

In response to the arguments advanced previously, the Examiner asserts that the individual references were argued, and not the combination.

Applicants have considered the Examiner's comments carefully, and traverse the rejection.

Applicants do not agree that they argued the references separately; rather, they feel that the references and the rejection were considered as a whole. They will do so again, and it is appropriate to begin with the French reference.

French deals with studies involving humans, a point that is important, and will be dealt with infra.

French discusses "idiopathic generalized epilepsy syndromes" and lists "absence, general tonic-clonic, and juvenile myoclonic epilepsy." French goes on to say that such

patients generally experience more than one seizure type, and usually require combination therapy, to make sure that each seizure type is treated. The final comment made by French is very relevant, i.e.:

> "Patients respond differently to AEDs for reasons that are still unclear, and it often not possible to quickly determine which agent or regimen will work."

"Black letter law" says that a reference must be considered as a whole, including those sections which are contrary to the Examiner's position. From French, one learns that this is a field fraught with uncertainty, and one should not make generalizations.

French should be considered in connection with Berendt, et al., J. Vet. Intern. Med., 13:14-20 (1999), a copy of which is attached. This reference teaches an investigation of whether or not the nomenclature of human epilepsy-including idiopathic epilepsy, can be extrapolated to dogs. See page 14, second column. Podele, in his editorial, "Epilepsy and Seizure Classification: a Lesson from Leonardo," J. Vet. Intern. Med., 13:3-4 (1999), a copy of which is attached, explains how this study shows the problems in rigorous application of definitions of human epilepsy to dogs, and, it is submitted, only strengthens the statements made in French about therapeutic uncertainty. If the conclusions in a human study are to be treated with care, much more care must be taken with extending them to dogs.

Ross does not alleviate these failings. Ross discusses the audiogenic seizure models (AGS), however, "AGS in rodents are an animal model for epilepsy." See the attached definition thereof, clearly speaking to the use of the model in rodents, and for epilepsy generally, NOT idiopathic epilepsy. Provided herewith is a copy of the definition of epilepsy utilized in the definition of AGS. It is also relevant that Ross never correlate AGS with idiopathic epilepsy. Rather, Ross discusses some of the manifestations of AGS, and as the literature shows, the symptoms Ross describes are not

at all limited to idiopathic epilepsy; rather, assuming one applies the AGS model to rodents as there is no support in the reference for extending it to any other animals, one induces symptoms, which may be treated; however, as French clearly show, one has to be very cautious in applying conclusions.

Turning to the primary reference, Bialer, it is uncontested that it teaches AWD 131-138 as a potential new, anti-epileptic drug; however, the results come from work on AGS induced mice, work on rats with absence epilepsy. Absence seizures are known to occur in several forms of epilepsy. Note Sega, a copy of which is attached, stating "absence seizures occur in both idiopathic and symptomatic epilepsy." The only other data involve the use of PTZ to induce seizures. By definition, if one known what causes the seizure, one does not have idiopathic epilepsy.

The fact is, Bialer does not lead one to idiopathic epilepsy in any way, manner or form, so one is hard pressed to see how it "meets the limitation of claim 12," as stated by the Examiner, at page 4 of the Office Action. Merely stating that a reference meets the claim is far from sufficient in the context of 35 U.S.C. § 103. As has been explained, supra, the generalizations regarding the secondary references, as set forth by the Examiner, do not serve to "fill in" the gaps left by Bialer. The references, taken collectively, do not suggest what is claimed.

With respect to the Examiner's statements at page 3 of the Office Action, AGS is caused by loud noise. Granted, it is not a cause chemical seizure, but the cause of the seizure is known – the loud noise. With respect to the Examiner's other arguments regarding treating dogs in other models, none of these have been correlated to idiopathic epilepsy. This could be difficult to do, as Thomas points out.

The rejection of claims 16 and 17, which relies on all of the references discussed supra, plus Thomas, cannot be sustained, as Thomas does not address the shortcomings of

the primary references. In re Kerkhoven, relied upon by the Examiner, is not relevant, since two references dealing with the treatment of idiopathic epilepsy, have not been provided – in fact, NONE have.

In view of the foregoing, withdrawal of the rejections and allowance of claims 12-17 and 19 is believed proper and is urged.

* * *

The Commissioner is hereby authorized to deduct the extension fee from the credit card. Form PTO 2038 is attached. Further, the Commissioner is hereby authorized to deduct any additional fee or credit any overpayment to our Deposit Account No. 50-0624, under Order No. NY-HUBR 1230-US (10312533) from which the undersigned is authorized to draw.

Dated: September 11, 2008

Respectfully submitted,

By _____
Norman D. Hanson
Registration No.: 30,946
FULBRIGHT & JAWORSKI L.L.P.
666 Fifth Avenue
New York, New York 10103
(212) 318-3000
(212) 318-3400 (Fax)
Attorney for Applicant

Attachments: References

Editorial

J Vet Intern Med 1999;13:3–4

Epilepsy and Seizure Classification: A Lesson from Leonardo

The classification of events that depend on the accuracy of observation is limited by the ability of the observer to describe and of the interpreter to decipher. Such is the case with the phenomenology of seizures and epilepsies. As Leonardo da Vinci wrote, *sapere vedere* ("learn to see"). Ease in distinguishing the occurrence of an epileptic seizure from the type of seizure event in domesticated animals varies based on the severity of the event, ranging from an unusual event experienced by the client to status epilepticus observed by the veterinarian. From this wide range of information, the daunting task arises to organize the myriad of descriptions provided to clinicians into a logical and understandable format. The ideal classification scheme should convey accurate and informative definitions to all levels of potential users, guide the clinician to evaluate the patient in terms of clinical and laboratory testing, allow different disciplines to use and understand the system, and allow flexibility in its adaptability and edification.[1] It is unlikely that one classification scheme will fulfill all of these criteria.

The current classification of epileptic seizures by the International League Against Epilepsy (ILAE)[2] is the principal determinant by which a human with epilepsy is placed on a specific antiepileptic drug. From this classification, patient data can be pooled from different institutions and environments for collaborative efforts and comparisons of research. Different pathogenic mechanisms can now be elucidated for the different seizure types. Eventually, by defining very discrete cohorts of epileptic patients, researchers will be able to examine a more homogeneous population of patients for possible genetic markers of inherited causes of epilepsy. Finally, clinicians are in a better position to offer a prognosis to the patient.

Epilepsy implies the recurrence of ictal manifestations over time, known as epileptic seizures.[3] Seizure types can be classified into 2 major categories, partial and generalized. This classification is based on the originating electroencephalographic activity and on the ensuing clinical changes (termed the electroclinical description).[2] Localization-related epilepsy is the result of focal electrical events in 1 cerebral hemisphere, resulting in partial epileptic seizures.[4] A partial seizure is classified based on the preservation (simple) or impairment (complex) of consciousness. Temporal lobe complex partial seizures are the most common epileptic seizure manifested in adult epilepsy. Infrequently, these initial partial seizures will secondarily generalize.[5] Generalized seizures are subdivided into convulsive (grand mal) and nonconvulsive (petit mal) seizures. Generalized seizures originate from both cerebral hemispheres.

Seizure etiology can basically be broken down into either unknown primary and known secondary or reactive causes.[6] The recent Revised International Classification of Epilepsies and Epileptic Syndromes[3] is based 1st on seizure type (localization-related versus generalized versus undetermined) followed by the epilepsy etiology. Idiopathic epilepsy is diagnosed when no underlying possible cause other than hereditary factors is found. Symptomatic epilepsies are the consequence of a known or suspected disorder of the central nervous system. Cryptogenic epilepsies are epilepsies that are suspected, but not proven, to be symptomatic. Note that all 3 etiologic classifications can occur with either seizure type. Accurate description, patient recall, and identification of intracranial pathology are imperative in this classification.

In this issue, Berendt and Gram[7] describe a study on the ability to apply "rigidly" the human epilepsy and seizures classification system to a case series study in dogs. A total of 63 previously untreated dogs with a history of 2 or more epileptic seizures, as described mostly by the owners, were evaluated for seizure type and etiology. The majority of dogs were classified as having partial seizures (65%), most commonly simple partial seizures. Almost all of the dogs (85%) with partial seizures developed secondary generalized seizures. The most commonly classified etiology was cryptogenic (45%), followed by idiopathic (25%), symptomatic (16%), and unclassified (14%). The authors conclude that the high frequency of partial seizures (mainly simple) with secondary generalization in epileptic dogs indicates the need to avoid using the term "generalized" seizures and to focus instead on whether the seizures are primarily or secondarily generalized.

The questions raised by the paper of Berendt and Gram[7] involve the accuracy of applying the seizure typing classification used for people to epileptic dogs, the interpretation of current terminology, the relationship between seizure etiology and seizure type, and the overall benefit of classifying seizures and epilepsy in canine epilepsy. These issues are at the heart of dealing with any epileptic animal and are of vital importance to our understanding and management of canine epilepsy. As such, conclusions on these issues must be the result of a carefully planned study design, proper scientific methodology, accurate result reporting, and valid comparisons between human and canine epilepsy. The authors should be applauded for their efforts to take on a study of such magnitude. Their results are intriguing and deserve careful analysis.

The 1st issue to address is how accurately one can determine the presence of partial seizures in dogs based mainly on owner observation. This decision requires accurate owner recall and interpretation by the clinician. Much subjectivity is involved in this process; for instance, distinguishing the prodrome (nonseizure period) from the aura (initial seizure period) is highly subjective. Several signs may occur in both situations, including attention-seeking, pacing, anxiety, restlessness, drooling, unusual expressions, and pupillary changes. Determining impaired consciousness can be difficult. Of the 78 clinical signs exhibited by dogs

classified with partial seizures in Berendt and Gram's paper,[7] 48 (61%) of the clinical signs were subjective interpretations by owners of events that could have occurred during either the prodrome or the aura stage. A list of the clinical signs associated with the onset of secondarily generalized seizures, along with information on the time period between the onset of initial signs and the onset of generalized seizures on and postictal changes, may have helped to elucidate this pattern. Pure simple partial motor seizures are often followed by focal motor weakness in people (Todd's paresis), a condition that was not described in the paper. In the absence of electroencephalographic data, videotape recording and subsequent critical analysis of all cases would enhance the validity of epilepsy studies. Without this information, conclusive evidence of the seizure categorization is lacking.

A 2nd issue is the difficulty in precisely applying the ILAE classification scheme to owner observed seizures in dogs, as evidenced by the fact that no dog with partial seizures was classified as having idiopathic epilepsy. This classification is in conflict with the human classification because human epileptics with localization-related epilepsy are often classified as idiopathic.[3] Similarly, all dogs diagnosed with cryptogenic epilepsy exhibited partial seizures, another classification choice that differs from the ILAE scheme. Symptomatic epilepsy designation requires documented disease or injury, a requirement that was not stringently adhered to in this study.

The 3rd issue raised by Berendt and Gram[7] is the relationship between seizure etiology and seizure type. Prospective studies for appropriately classifying all animals into a disease category require that all of the animals receive identical diagnostic evaluations. In particular, brain imaging is an important diagnostic tool to identify occult intracranial lesions. In a prospective study of 50 epileptic dogs that underwent extensive diagnostic testing (including magnetic resonance imaging scans), 37% of dogs between the ages of 1 and 7 years of age that had a normal neurologic examination had a definitive diagnosis established.[8] Moreover, older dogs that had generalized seizures as the only clinical sign but had a normal examination may have a "silent" cortical lesion.

Finally, what is the overall benefit of classifying seizures and epilepsy in canine epilepsy as compared with human epilepsy? It is not surprising that many differences exist between epileptic humans and dogs: dogs have a much differently wired brain than people have, dogs are more highly inbred, they are less exposed to certain precipitating factors (ie, head trauma), and they cannot provide symptomatologic recall of seizure events. Yet important similarities do exist between the 2 species: both exhibit partial and generalized seizures, an inherited basis for idiopathic epilepsy most likely exists for both, and response to antiepileptic drug therapy may be dependent on seizure type in both species. Thus, seizure and epilepsy classification is needed to help further the understanding of canine epilepsy and to provide a foundation for clear communication between specialists, general practitioners, and owners. This paper helps to heighten the awareness of the continuing need to further categorize and study partial seizure disorders in canine epilepsy. Accurate information is needed to advance our goals of identification and treatment of this prevalent disease through collaborative, prospective studies. We can all benefit from Leonardo's lesson: *sapere vedere.*

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Michael Podell, MSc, DVM
Diplomate ACVIM, Neurology
Associate Professor
Ohio State University
Veterinary Clinical Sciences
1107 Veterinary Teaching Hospital
Columbus, OH 43210
e-mail: podell.1@osu.edu

Definition: audiogenic seizure from Online Medical Dictionary

audiogenic seizure

A reflex seizure precipitated by loud noises, rare in humans. Audiogenic seizures in rodents are an animal model of epilepsy.

(05 Mar 2000)

Previous: Auchmeromyia luteola, auctorum, auctorum non, audile, audio-, audioanalgesia, audiogenic
Next: audiogram, audiologist, audiology, audiometer, audiometric

epilepsy

<disease, neurology> The paroxysmal transient disturbances of brain function that may be manifested as episodic impairment or loss of consciousness, abnormal motor phenomena, psychic or sensory disturbances or perturbation of the autonomic nervous system.

Symptoms are due to paroxysmal disturbance of the electrical activity of the brain. On the basis of origin, epilepsy is idiopathic (cryptogenic, essential, genetic) or symptomatic (acquired, organic). On the basis of clinical and electroencephalographic phenomenon, four subdivisions are recognised:

1. Grand mal epilepsy (major epilepsy, haut mal epilepsy) subgroups: generalised, focal (localised), jacksonian (rolandic)

2. Petit mal epilepsy

3. Psychomotor epilepsy (temporal lobe epilepsy, psychic, psychic equivalent or variant) subgroups: psychomotor proper (tonic with adversive or torsion movements or masticatory phenomena), automatic (with amnesia) and sensory (hallucinations or dream states or d,j. Vu)

4. Autonomic epilepsy (diencephalic), with flushing, pallor, tachycardia, hypertension, perspiration or other visceral symptoms.

Synonym: epilepsia.

Origin: Gr. Epilepsia = seizure

(14 May 1997)

Previous: epilemmal ending, epilepidoma, epilepsia, epilepsia partialis continua
Next: epilepsy, absence, epilepsy, complex partial, epilepsy, frontal lobe

J Vet Intern Med 1999;13:14–20

Epilepsy and Seizure Classification in 63 Dogs: A Reappraisal of Veterinary Epilepsy Terminology

Mette Berendt and Lennart Gram

The human definitions of epilepsy and seizure classification were applied rigidly to epileptic dogs to investigate whether the distribution of the seizure types and epilepsies of dogs is comparable to that of human beings. Sixty-three dogs were referred because of recurrent (>2) epileptic seizures. Only dogs without previous or ongoing antiepileptic treatment were included. All dogs had a physical and neurologic examination and blood work that included a CBC and a biochemical profile. All owners were asked to complete a questionnaire, focusing on seizure development. In addition, video recordings of suspected seizure episodes were analyzed if available. In the majority of dogs where an intracranial lesion was suspected, a computerized tomography scan was performed. Sixty-five percent of the dogs experienced partial seizures with or without secondary generalization and 32% exhibited primary generalized seizures; in 3% of the dogs the seizures could not be classified. Twenty-five percent of these cases were classified as idiopathic, 16% as symptomatic, and 45% as cryptogenic epilepsy; in 14% of these a classification was not possible. Applying human definitions, the distribution of seizure types and epilepsy classifications in these dogs differed widely from those in previous reports of canine epilepsy, where generalized seizures and idiopathic epilepsy were most frequently reported. However, our findings are consistent with the results of several large studies of human epilepsy patients. In dogs with epilepsy, closer attention must be given to the detection of a partial onset of seizures. In this study, detailed questioning of the owners and when possible analysis of video recorded seizures, proved to be sufficient for diagnosing seizures with a partial onset in a significant number of dogs. Partial onset of seizures may be an indication of underlying cerebral pathology. Some adjustments of veterinary epilepsy terminology are suggested.

Key words: Brain; Cryptogenic seizure; Epilepsy classification; Seizure types.

In veterinary medicine, it is a common belief that the vast majority of dogs with epilepsy experience generalized seizures, most frequently in the form of convulsions.[1–9] The majority of canine epilepsies have been considered idiopathic (ie, primary generalized epilepsy of unknown cause but with possible familial predisposition).[4,9] Although veterinary investigators recognize that localized motor activity preceding convulsions is indicative of a partial onset with secondary generalization, the occurrence of an aura appears to be considered a preictal event, unrelated to the subsequent seizure, with the seizure classified as a generalized seizure.

In human classification of epileptic seizures, an aura is recognized/classified as a simple partial seizure, which may or may not progress into secondary generalization in the form of convulsions.[10] The word *aura* (Gr. *aura*=breeze) was first introduced by the Greek physician Galén after having heard a patient describe this sensation as a cold breeze. The aura represents the initial activation of a single group of neurons and is often reflected clinically in a stereotyped sensation, eg, sensory, visual, auditory, or vertiginous in human epilepsy patients, perceived as a warning sign. During the aura (the simple partial seizure), consciousness is unimpaired. In human epileptology, 53–57% of patients are diagnosed with partial seizures with or without secondary generalization.[11–13]

Human classification of epilepsies deals with three categories: (1) *idiopathic* epilepsy, presenting with primary generalized seizures, often starting early in life and frequently involving a hereditary predisposition and with no underlying cause; (2) *symptomatic* epilepsy, starting at any point in life, characterized by partial seizures with or without secondary generalization, and caused by a known disorder of the central nervous system (CNS); and (3) *cryptogenic* (Gr. *cryptos*=hidden) epilepsies, which are suspected to be symptomatic, but where no etiology is known.[14]

Veterinary epilepsy nomenclature has borrowed extensively from its human counterpart, but for a number of terms important differences exist in their definitions and interpretations. The purpose of this study was to apply the definitions used in human epileptology to dogs with epilepsy and to investigate whether the epilepsies and epileptic seizures of dogs have a distribution similar to those in humans.

Material and Methods

Inclusion Criteria

Dogs were presented to the Royal Veterinary and Agricultural University of Copenhagen from September 1993 to August 1994 and September 1995 to December 1996 with a primary complaint of recurrent (>2) epileptic seizures. Only dogs without previous or ongoing antiepileptic treatment were included in the study. Dogs having an extracranial cause for their seizures were excluded from the study.

Investigations

Investigations for each dog included a questionnaire to the owner focusing on seizure development (owners also were encouraged to provide video recordings of suspected seizure episodes), physical and neurologic examinations, and routine CBC and serum biochemistry. A computerized tomography (CT) scan was performed on 6 dogs in

From the Small Animal Hospital, Department of Clinical Studies, The Royal Veterinary and Agricultural University of Copenhagen, Copenhagen, Denmark (Berendt); and the Department of Neurology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark (Gram).

Reprint requests: Mette Berendt, DVM, PhD, Small Animal Hospital, Department of Clinical Studies, The Royal Veterinary and Agricultural University of Copenhagen, Bülowsvej 13, DK-1870 Frb. C. Copenhagen, Denmark. e-mail: mab@kvl.dk.

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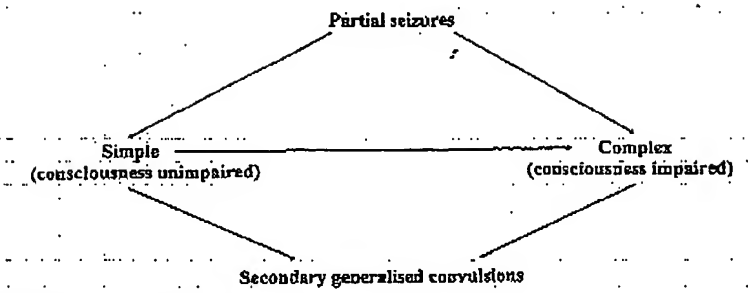

Fig 1. Way for a partial seizure to develop into secondary generalization.

which the neurologic examination indicated an intracranial lesion. Dogs that were euthanized during the study were examined postmortem.

Classification of Seizures

As in human epileptology, prodromes were defined as manifestations preceding a seizure in epileptic individuals by several hours or days, often a disturbance of mood or behavior, less frequently such subjective symptoms as headache, or rarely other phenomena. Epileptic prodromes usually reflect a preictal increase in excitability of an epileptogenic focus or of the entire brain. They must therefore be carefully distinguished from auras, which represent the onset of a seizure.[15]

Seizures generalized from the onset were classified as primary generalized seizures. Seizures with a focal onset were defined as a simple partial seizure (aura) when consciousness was not impaired or a complex partial seizure when consciousness was impaired. Simple partial seizures may develop into complex partial seizures, and both types of partial seizures may secondarily generalize and develop into convulsions, or secondary generalized seizures. The development of partial seizures is illustrated in Figure 1.

Classification of Epilepsies

Dogs with an early onset of primary generalized seizures and a normal neurologic examination were classified as having idiopathic epilepsy. Family predisposition was also considered for this group. Symptomatic epilepsy was diagnosed in dogs having partial seizures, with or without secondary generalization, and where the epilepsy was the consequence of a known disorder of the CNS irrespective of the animal's age. Dogs experiencing partial seizures with or without secondary generalization but where patient history, neurologic examination, and diagnostic testing failed to demonstrate a focal etiology were suspected of symptomatic epilepsy, and their epilepsy was classified as cryptogenic.

Results

Signalment and Diagnostic Investigations

Of the 63 dogs evaluated, 25 (40%) were intact females, 37 (59%) were intact males, and 1 (1%) was a castrated male. The study population comprised 26 different breeds and mixed breeds. Mixed breeds, Labrador Retrievers, and Boxers were most frequently represented. Forty-seven dogs were ≤4 years of age at seizure onset. A significant proportion of them had partial seizures.

Complete blood counts and serum biochemical analyses were within normal limits in all 63 dogs. The neurologic examination was abnormal in 8 dogs. The abnormalities included signs of dysfunction of 1 more cranial nerves, postural deficits, and depressed mentation. Of the 6 dogs examined by CT scan, 3 had a space-occupying lesion and 3 had a normal scan. Postmortem examinations were performed on 9 dogs that were euthanized during the study. The postmortem examination revealed an astrocytoma in 3 dogs, granulomatous meningoencephalomyelitis in 1 dog, canine distemper in 1 dog, and meningitis in 1 dog; 3 dogs with a normal examination. The signalment, clinical data, and seizure and epilepsy classification of the 63 dogs are provided in Table 1.

Classification of Seizures

Seven dogs (11%) suffered from prodromes prior to the onset of seizures. Five of these dogs experienced primary generalized seizures. Prodromes lasted for 1–24 hours, during which the dogs would cling to the owners and express anxiety (4 dogs), be restless (2 dogs), and eat the carpet (1 dog). All owners stated that they could consistently predict a forthcoming seizure by changes in the dog's behavior.

Forty-one (65%) of the dogs experienced partial seizures with or without secondary generalization, and 20 (32%) of the dogs suffered from primary generalized seizures (no evidence of a partial onset). In 2 dogs (3%), the seizures could not be classified. The owners of 28 dogs (68%) with partial seizures reported a simple partial onset and no impairment of consciousness (aura), whereas in 11 dogs (27%) the onset was complex, ie, consciousness was impaired. In 2 dogs (5%), it was not possible to determine whether the seizure had a simple or complex onset. Because of obvious problems with the evaluation of subtle and or rapid changes in the consciousness of dogs, we did not try to identify dogs with a development of simple partial into complex partial seizures. The partial seizures in 35 (85%) of the dogs progressed into secondary generalization in the form of convulsions. The 6 dogs that did not experience secondary generalization all had complex partial seizures. Seizure distribution is depicted in Figure 2.

The clinical signs experienced during partial seizures included seeking attention from the owner (12 dogs); motor symptoms such as rythmic contractions or flexion of a specific limb, occurring in a repetitive manner from seizure to seizure, turning of the head always in the same direction, tonic opening of the jaw, and head tremor (12 dogs); anx-

Table 1. Clinical data from 63 dogs with recurrent epileptic seizures.

Dog Breed	Sex	Age at Onset (years)[a]	Neurologic Examination[b]	Seizure Classification	Epilepsy Classification
1. Dachshund	M	3.41	N	Primary generalized[c]	Idiopathic
2. Fox Terrier	M	13.00	N	Primary generalized	
3. Cocker Spaniel	M	2.25	N	Partial, secondary generalized[d]	Cryptogenic
4. Alsatian	M	8.00	A	Partial, secondary generalized	Symptomatic
5. Poodle	F	1.00	N	Partial, secondary generalized	Cryptogenic
6. Labrador Retriever	M	0.58	N	Primary generalized	Idiopathic
7. Swiss Mountain Dog	M	1.50	A	Partial, secondary generalized	
8. Mixed	F	0.92	N	Primary generalized	Idiopathic
9. Alsatian	F	1.58	N	Complex partial	Cryptogenic
10. Dalmatian	M	1.83	N	Primary generalized	Idiopathic
11. Wire Haired Pointer	M	1.58	N	Primary generalized	Idiopathic
12. Boxer	F	4.50	A	Complex partial	Symptomatic
13. Dobermann Pincher	M	1.00	N	Complex partial	Cryptogenic
14. Springer Spaniel	M	1.00	N	Primary generalized	Idiopathic
15. Cocker Spaniel	M	1.75	N	Partial, secondary generalized	Cryptogenic
16. Labrador Retriever	F	1.00	N	Partial, secondary generalized	Cryptogenic
17. King Charles Spaniel	M	1.58	N	Partial, secondary generalized	Cryptogenic
18. Mixed	M	2.17	N	Primary generalized	Idiopathic
19. Springer Spaniel	M	1.08	N	Primary generalized[e]	Idiopathic
20. Rottweiler	M	2.08	N	Partial, secondary generalized	Cryptogenic
21. Wire Haired Pointer	F	2.00	N	Primary generalized[e]	Idiopathic
22. Golden Retriever	M	1.00	N	Partial, secondary generalized	Cryptogenic
23. Mixed	M	Unk	N	Primary generalized[e]	
24. Labrador Retriever	F	2.83	N	Partial, secondary generalized	Cryptogenic
25. Cocker Spaniel	M	9.83	A	Complex partial	
26. Golden Retriever	M	1.33	N	Partial, secondary generalized[e]	Cryptogenic
27. Giant Schnauzer	M	9.00	A	Partial, secondary generalized	Symptomatic
28. Bernese Mountain Dog	M	2.67	N	Primary generalized[e]	Idiopathic
29. Mixed	F	Unk	N	Partial, secondary generalized	
30. Beagle	F	Unk	N	Partial, secondary generalized	
31. Beagle	M	2.50	N	Partial, secondary generalized	Cryptogenic
32. Boxer	F	0.50	N	Partial, secondary generalized	Cryptogenic
33. Alsatian	F	6.00	N		
34. Alaskan Malamute	F	1.50	N	Partial, secondary generalized	Cryptogenic
35. Mixed	F	3.58	A	Primary generalized	Symptomatic
36. Mixed	M	7.67	N	Primary generalized	Idiopathic
37. Rottweiler	F	2.25	N	Partial, secondary generalized	Cryptogenic
38. Boxer	M	6.00	A	Partial, secondary generalized	Symptomatic
39. Labrador Retriever	M	5.00	N	Primary generalized	
40. Pekingese[e]	F	0.75	N	Partial, secondary generalized[d]	Symptomatic
41. Great Dane	F	1.00	N	Primary generalized	Idiopathic
42. Boxer	M	0.50	N	Primary generalized	Idiopathic
43. Mixed	M	3.00	N	Primary generalized	Idiopathic
44. Boxer	M	3.25	A	Partial, secondary generalized[d]	Symptomatic
45. Dalmatian	M[f]	3.50	N	Partial, secondary generalized[d]	Cryptogenic
46. Labrador Retriever	M	1.50	N	Partial, secondary generalized	Cryptogenic
47. Pomeranian	F	0.17	N	Partial, secondary generalized	Cryptogenic
48. Labrador Retriever	M	1.00	N	Partial, secondary generalized	Cryptogenic
49. Karelian Bear Hound[e]	M	5.50	N	Partial, secondary generalized	Symptomatic
50. Bouvier des Flandres	M	3.08	N	Partial, secondary generalized	Cryptogenic
51. Alsatian	F	2.00	N	Partial, secondary generalized	Cryptogenic
52. Beagle	F	1.00	N	Partial, secondary generalized	Cryptogenic
53. Pekingese	M	3.25	N	Complex partial	Cryptogenic
54. Labrador Retriever[e]	F	1.58	N	Partial, secondary generalized	Cryptogenic
55. Golden Retriever	F	2.50	N	Partial, secondary generalized	Cryptogenic
56. Labrador Retriever	M	1.42	N	Partial, secondary generalized	Cryptogenic

Table 1. Continued.

Dog Breed	Sex	Age at Onset (years)[a]	Neurologic Examination[b]	Seizure Classification	Epilepsy Classification
57. Fox Terrier	M	1.50	N	Partial, secondary generalized	Cryptogenic
58. Shetland Sheepdog	F	2.17	N	Partial, secondary generalized	Cryptogenic
59. Mixed	F	1.33	N	Partial, secondary generalized[c]	Symptomatic
60. Rottweiler	M	1.00	N	Primary generalized	Idiopathic
61. Mixed	M	6.50	A	Complex partial	Symptomatic
62. American Cocker Spaniel	F	5.00	N		
63. Dachshund	F	4.00	N	Primary generalized	Idiopathic

[a] Unk = unknown.
[b] N = normal; A = abnormal.
[c] Prodromes.
[d] Complex partial onset with secondary generalization.
[e] History of severe head trauma preceding seizure development.
[f] Male castrate.

iety (10 dogs); trembling (9 dogs); drooling (4 dogs); vomiting (4 dogs); incoordination (7 dogs); sitting down/loosing tone in the pelvic limbs (7 dogs); a staring look (6 dogs); restlessness (5 dogs); and dilation of pupils (2 dogs).

The 11 dogs experiencing complex partial seizures with or without secondary generalization were characterized by a detectable impairment of consciousness, often involving automatisms. The dogs appeared disoriented, were unable to recognize their owners, and unable to respond to commands. Some dogs would express signs such as headpressing, and others seemed to experience episodes with a change in perception. Such episodes included following imaginary objects, unprovoked aggression, and unmotivated barking, behavior that could not be distracted and that would occur repeatedly and was stereotyped in the individual dog. The signs in the 6 dogs that had complex partial seizures without secondary generalization were dominated by confusion and abnormal behavior. Two dogs were bewildered, running around the house drooling, shaking, and barking; 1 dog followed imaginary objects and showed unprovoked agression combined with atonia of 1 hind limb; 1 dog expressed head tremor and confusion; 1 dog had localized tonic activity of 1 hind limb combined with confusion; 1 dog was headpressing and unable to respond to commands. The dogs were unable to recognize their owners while seizuring. The duration of the seizures was up to 2 minutes. The lack of secondary generalization in these dogs allowed for a more pronounced development of behavioral disturbances than in the 5 dogs experiencing secondary generalization. The dogs experiencing complex partial seizures without secondary generalization had a higher seizure frequency and tendency to cluster seizures than did the dogs with secondary generalisation.

In all 63 dogs, the postictal signs were dominated by initial confusion followed by fatigue and often deep sleep. The duration of these symptoms typically ranged from 2 to 30 minutes. In 4 dogs, the owners described that the dog would appear depressed for a couple of days following seizures. Overall, no correlation was observed between the type, intensity, or duration of seizures and the duration of the postictal phase.

Classification of Epilepsies

The classification of the epilepsies for the 63 dogs of the study is presented in Table 2. Combining early onset of seizures (≤4 years of age) with no evidence of a partial onset and taking family predisposition into consideration,

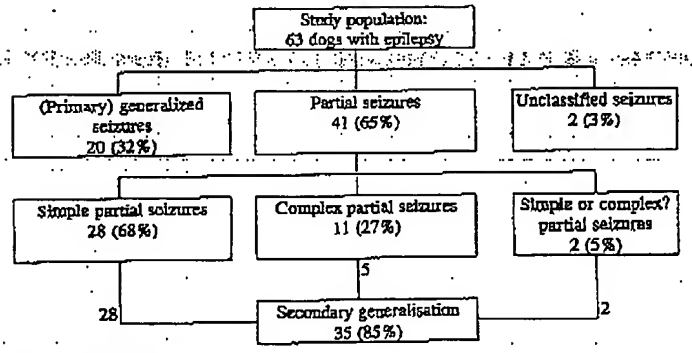

Fig 2. Seizure types and development in 63 dogs.

Table 2. Classification of the epilepsies in 63 dogs.

Epilepsy Type	Criteria	No. Dogs
Idiopathic	Familial predisposition Early onset of seizures No partial seizures Normal diagnostic workup	16 (25%)
Symptomatic	Caused by a known intracranial disorder Partial seizures Abnormalities on neurologic examination (late onset combined with abnormalities on neurologic examination is highly suspect)	10 (16%)
Cryptogenic	Partial seizures Symptomatic cause suspected (but unconfirmed) Abnormalities on neurologic examination	28 (45%)
Unclassified	None of the above	9 (14%)

15 dogs were classified as having idiopathic epilepsy. One dog with late seizure onset had a normal CT scan and a normal brain at autopsy. This dog also was classified as having idiopathic epilepsy, bringing the total up to 16 (25%). Ten dogs (16%) were classified as having symptomatic epilepsy on the basis of a known intracranial disease (confirmed at CT scan or postmortem examination), a focal intracranial disorder as a consequence of previous severe head trauma, or the finding of focal abnormalities on the neurologic examination. In 28 dogs (45%) experiencing partial seizures, a symptomatic cause was suspected but not confirmed, resulting in classification of cryptogenic epilepsy. In 9 dogs (14%), classification of the epilepsy was not possible because of a lack of information from the owner about seizure signs (kennel dogs: 2), unknown age at seizure onset and present age (3 dogs from an animal shelter), the occurrence of late seizure onset combined with apparent primary generalized seizures, or the foresence of a partial seizure without a demonstrable lesion on CT scan or postmortem examination.

Discussion

Seizure Types

In this study, 65% of the dogs suffered from partial seizures with or without secondary generalization, 32% experienced primary generalized seizures, and in 3% the seizures could not be classified. These results are in contrast with those of previous studies, where the most frequent type of seizures reported were the generalized seizures,[2,4–6,16,17] apparently without differentiation between primary and secondary generalized seizures. The distribution of seizure types observed in the present study is in accordance with the findings of 3 recent large surveys of seizure types in random groups of human patients. According to these studies, partial seizures were observed in 53–57% of human epilepsy patients, primary generalized seizures occurred in 27–40%, and in 3–18% of patients seizures could not be classified.[11–13] When applying the definitions used in human epileptology, similarity exists between humans and the dogs of this study with regards to seizure types and epilepsy classification. Had previous studies of dogs incorporated the same definitions as those used in the present study, the results might have been similar.

Veterinary versus Human Epilepsy Nomenclature

Because veterinary epilepsy nomenclature makes use of its human counterpart, it is important to clarify certain basic terms used to describe human epilepsy. In veterinary medicine it is common to describe the epileptic seizure as a sequence of events: the prodromal phase, the preictal phase (often referred to as the aura), the subsequent ictus, and the postictal phase.[4,6,9,18] It is common to refer to generalized seizures in dogs without indicating whether they are of partial origin with subsequent secondary generalisation or whether they are generalized from the start, ie, primary generalized seizures.

In humans, prodromes refer to a long-lasting (hours to days) change of mind in the form of anxiety, irritability, withdrawal, and other emotional aberrations. Prodromes are not considered part of the seizure and are not related to abnormal electrical activity in the electroencephalogram (EEG).[19,20]

An aura is that portion of the seizure that occurs before consciousness is lost and thus is synonymous with a simple partial onset of a seizure. Because an aura represents an ictal rather than preictal event, it is indicative of a focal seizure onset, which may or may not develop into secondary generalization (convulsions).[19,20] An isolated aura thus represents a simple partial seizure (the entire seizure). The usual duration of an aura is seconds to a few minutes, and an aura may not always cause detectable abnormal electrical activity in the scalp EEG.[20] Simple partial seizures may develop into complex partial seizures when consciousness becomes impaired. Complex partial seizures frequently involve automatisms, which are defined as involuntary automatic motor behavior, ie, lip smacking or chewing, occurring at the time that consciousness is impaired.

Consequently, what in veterinary medicine is usually described as a typical epileptic seizure, evolving through the phases mentioned above, actually describes a patient experiencing prodromes followed by a partial seizure onset evolving into secondary generalization, clinically expressed as convulsions. The seizure is followed by a postictal phase, often consisting of reorientation with or without deep sleep.

In humans, the aura may present as changes in perception of the surroundings in the form of distortions of sound or of gustatory or olfactory sensations, change in spatial dimensions of surroundings, distortion of time sense, sensation of unreality, detachment, or depersonalization, pseudohallucinations, fear, and sensations as if a naive experience has been experienced before (déjà vu).[20] Localized motor symptoms may also but less frequently constitute the symptomatology of an aura. As for epileptic seizures in general, the signs observed during partial onset of seizures characteristically are extremely stereotyped in a given individual. In the present study, the onset of partial seizures always followed an identical pattern, characteristic for a

given patient, but was often reported by the owner only after thorough questioning.

A number of the rather delicate clinical signs described in humans can never be confirmed in animals. However, if questioned, dog owners frequently reported subtle changes in their animals' behavior. Some of these changes in behavior were caused by a distortion of perception, either immediately preceeding convulsions or existing as an isolated phenomenon, constituting the entire seizure. Brief, recurrent, stereotyped changes in behavior, motor signs, or autonomic clinical signs with or without impairment of consciousness should be recognized as a possible clinical expression of an epileptic focus, giving rise to seizures with a partial onset.

Experimental evidence indicates that dogs may indeed suffer from simple or complex partial seizures, manifested with a variety of clinical signs other than simple motor malfunctions.[21] In both veterinary and human epileptology, partial seizure onset can be subtle and followed by a rapid secondary generalization, making it difficult to detect the partial onset.[22]

Koutinas et al[9] claimed that in dogs a correlation exists between the duration of the postictal phase and the type, intensity, or duration of the seizure. This correlation has not been seen in humans and was not observed in the present study.

Types of Epilepsies

Twenty-five percent of the dogs in this study were classified as having idiopathic epilepsy, and 61% were classified with symptomatic/cryptogenic epilepsy. This distribution differs from that in a recent study in dogs, where 41% were classified as having idiopathic epilepsy, 49% as having symptomatic epilepsy, and 10% as having seizures secondary to a reaction of a normal brain to transient systemic insult or physiologic stress, defined as, reactive epileptic seizures.[7] Although only 82% of the dogs in this recent study fulfilled the criterion for epilepsy (>1 seizure), the distribution between partial and generalized seizures was similar, whether the dogs were classified as having idiopathic or symptomatic epilepsy.[7] Because in the vast majority of cases a seizure with a partial onset indicates an underlying structural cause, one would have expected a much higher frequency of partial seizures in the group of dogs classified as having symptomatic epilepsy. The same arguments are valid for one of the most recent studies of epilepsy in 54 Labrador Retrievers presumed to suffer from idiopathic epilepsy.[8] Signs of a partial seizure onset, either as focal motor events or in the form of an aura, was however observed in 20 (37%) of the dogs. Consequently, partial seizures seem to occur more frequently in dogs than has so far been perceived. Thus, the frequency of idiopathic epilepsy in dogs may have been overestimated.

The distribution of the dogs in the present study between the two main categories of epilepsy is consistent with the results of two recent human studies. In one study of 8,570 patients, 27% had idiopathic and 73% had symptomatic epilepsy.[23] In the other investigation of 200 patients, 23% had idiopathic and 55% had symptomatic epilepsy.[24]

In the present study, 45% of the dogs were classified as suffering from cryptogenic epilepsy; the partial onset of their seizures was highly suggestive of an underlying focal intracranial pathology. The immense progress in imaging techniques, especially the increasing application of magnetic resonance scanning, has disclosed an increasing number of structural causes for epilepsy that were not previously recognized. For instance, the application of magnetic resonance scanning increased the percentage of patients classified with symptomatic epilepsy in a study by King et al.[24] In addition, magnetic resonance scanning has made it possible to identify cerebral pathologic changes, such as neuronal migration disorders in the form of focal cortical dysplasia and focal subcortical heterotopias, that are not detected by CT scanning. In humans, these changes are probably the most common focal neurodevelopmental disorders associated with partial, often refractory epilepsy.[25–27] Refining neuroimaging techniques in humans has resulted in an increase in epilepsies classified as symptomatic and a concomitant decrease in the proportion of cryptogenic and idiopathic epilepsies. This same trend may also be seen in dogs, although initial detection of partial onset of epileptic seizures is of primary diagnostic importance.

In this study, the EEG was not included as a diagnostic aid. With an EEG, it might have been possible to further determine the identity of the seizures described by the owners and recorded on video. EEG analysis might have changed the seizure classification, especially in dogs where detailed information regarding seizure development was lacking and in dogs experiencing partial seizures with very rapid secondary generalization.

Conclusions

In veterinary epileptology, the term "generalized seizures" should be avoided. Each seizure should be categorized as a primary or a secondary generalized seizure because this characterization is crucial for understanding seizure development. If the seizure has a partial onset, given adequate technology, an underlying cerebral pathology is expected. In the present study, there was a high frequency of partial seizures in dogs, comparable to what is observed in humans. This finding underscores the importance of acknowledging indications of a partial seizure onset in the form of subtle and transient clinical signs, which may go undetected if the historical investigation is not thorough.

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Absence Seizures

Email to a Colleague

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Synonyms and related keywords: petit mal seizures, generalized seizures, idiopathic generalized **epilepsy**, symp generalized **epilepsy**

AUTHOR INFORMATION

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Author Information Introduction Clinical Differentials Workup Treatment Medication Follow-up Miscellaneous Pictures Bibliography

Author: **Scott Segan, MD**, Attending Neurologist, Clinical Assistant Professor, New York Colle Osteopathic Medicine, Division of Neurology, St Barnabas Hospital, Bronx, NY

Scott **Segan**, MD, is a member of the following medical societies: American Academy of Neur and American **Epilepsy** Society

Editor(s): **Edward B Bromfield, MD**, Associate Professor of Neurology, Faculty Member, Divi Sleep Medicine, Harvard Medical School; Chief, Division of EEG, **Epilepsy** and Sleep Neurol Consulting Neurologist, Brigham and Women's Hospital; **Francisco Talavera, PharmD, PhD**, Pharmacy Editor, eMedicine; **Jose E Cavazos, MD, PhD**, Assistant Professor, Departments c Medicine (Neurology) and Pharmacology, University of Texas Health Science Center at San A **Selim R Benbadis, MD**, Professor of Neurology, Director of Comprehensive **Epilepsy** Progra Departments of Neurology and Neurosurgery, University of South Florida College of Medicine General Hospital; and **Nicholas Lorenzo, MD**, Chief Editor, eMedicine Neurology; Consulting Neurology Specialists and Consultants

Disclosure

INTRODUCTION

Background: Absence seizures are a type of generalized seizures. They were first described in 1705, and later by Tissot in 1770, who used the term petit access. In 1824, Calmeil used the absence. In 1935, Gibbs, Davis, and Lennox described the association of impaired consciousr 3-Hz spike-and-slow-wave complexes on electroencephalograms (EEGs).

Absence seizures occur in both idiopathic and symptomatic generalized epilepsies. Among the idiopathic, or primary, generalized epilepsies (ie, with age-related onset), absence seizures ar childhood absence **epilepsy** (CAE, or pyknolepsy), juvenile absence **epilepsy** (JAE), and juve myoclonic **epilepsy** (JME, or impulsive petit mal seizures). The seizures in these conditions a typical absence seizures and usually associated with 3-Hz spike-and-slow-wave complexes or In CAE, seizures are frequent and brief, lasting just a few seconds (pyknoleptic). Some childre have hundreds of such seizures per day. In other epilepsies, particularly those with an older a onset, the seizures can last several seconds to minutes and may occur only a few times a day nonpyknoleptic or spanioleptic absence seizures). Myoclonic and tonic-clonic seizures may al present, especially in syndromes with an older age of onset. In these syndromes, the discharg frequency may be faster than 3 Hz.

In the symptomatic generalized epilepsies, absence seizures are often associated with slow s wave complexes of 1.5-2.5 Hz; these are also called sharp-and-slow-wave complexes. These are termed atypical absence seizures.

Pathophysiology: The etiology of idiopathic epilepsies with age-related onset is genetic. Abo 40% of patients with these epilepsies have a family history of **epilepsy**; concordance in mono twins is 75%. Family members may have other forms of idiopathic or genetic **epilepsy** (eg, fet convulsions, generalized tonic-clonic [GTC] seizures).

Several animal models demonstrate the genetic basis for absence seizures. A strain of Wistar genetic absence **epilepsy** rats from Strasbourg (GAERS), is a polygenetic model in which all have clinical seizures consisting of a behavioral arrest with twitching of facial muscles. This is associated with bilateral synchronous spike-wave discharges. Several single-gene loci in mice mutated, result in generalized spike-wave **epilepsy**. The tottering (chromosome 8), lethargic (chromosome 2), stargazer (chromosome 15), mocha (chromosome 10), and ducky (chromos loci all have generalized 6-per-second spike-wave EEG paroxysms that are associated with cl seizures consisting of behavioral arrest. All types respond to ethosuximide (ETX), but the und cellular mechanisms for the generation of the discharges are not identical.

Several mutations of genes which encode protein subunits in various ion channels have been patients and family members with idiopathic epilepsies. Some forms of JME and absence epil have been shown to result from mutations in Ca^{++} channels.